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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/712,819	11/13/2000	Fred J. Stevens	0003/00537	9146

7590 06/16/2004

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/712,819	STEVENS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7,10,14-16 and 23-34* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,5 7 and 10* is/are allowed.

6)☒ Claim(s) *15,16,23-30,32 and 34* is/are rejected.

7)☒ Claim(s) *31 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/21/04 has been entered.

2. Claims 1-2, 5, 7, 10, 14-16 and 23-34 are pending.

3. Claim 14 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-2, 5, 7, 10, 15-16 and 23-34 are being acted upon in this Office Action.

5. The disclosure is objected because of the following informality. "foudn" on page 14, line 14 should have been "found".

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 23-30, 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain, the method comprising: a) identifying the SMA or LEN mutation in the amino acid sequence of the kappa-IV light chain that lead to fibril formation, b) substituting each mutation for Ala or proline into said LEN or SMA to identify the residues of a peptide that contribute to fibril formation; c) synthesizing peptides spanning most of the light chain variable region that interacts with an endoplasmic reticulum chaperone selected from the group consisting of Bip, Hsp 70 and combinations thereof; d) determining the Variable light chain (V_L)-derived peptides for their ability to inhibit fibril formation in vitro wherein the peptides are selected from the group consisting of TDFTLTI (SEQ

ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKSR (SEQ ID NO: 13) and combination thereof and e) inhibiting fibril formation by inserting the said peptide in to the light chain variable domain as set forth in claims 1, 2, 5, 7, 10, 15 and 16, **does not** reasonably provide enablement for (1) a method for minimizing the aggregation tendencies of any or all amyloid forming proteins, the method comprising identifying any or all "submotifs" in primary structure of the protein that induce fibril formation, and interacting any or all "biological molecule inhibitor" with said critical "submotifs" so as to stabilize the normal conformation of the protein, by mutating any amino acid sequence of said protein, (2) a method for minimizing the aggregation tendencies of any or all amyloid forming proteins such as antibody constant domain, transthyretin, beta-2 microglobulin, serine protease inhibitors and crystalline, the method comprising identifying any or all "submotifs" in primary structure of the protein that induce fibril formation, and interacting any or all "biological molecule inhibitor" with said critical "submotifs" so as to stabilize the normal conformation of the protein, (3) the said method wherein any or all inhibitors interacts with the human kappa-IV light chain between residue position numbers "60 and 83" of the light chain, (4) The said method wherein the peptide "having" the amino acid sequence Phe_{71}-Thr_{72}-Leu-$_{73}$-Thr_{74},-Ile_{75}-Ser_{76}-Ser_{77} (SEQ ID NO: 1), (5) a method for preventing fibril assembly of human kappa-IV immunoglobulin, the method comprising a) identifying the residues of peptide that contribute to fibril formation by mutating the amino acid sequence of human kappa-IV immunoglobulin and blocking said fibril formation by inserting any or all biological molecules into the amino acid sequence. (6) A method for minimizing the aggregation tendencies of human kappa-IV immunoglobulin light chain protein in a cell, the method comprising a) expressing any or all protein in a cell, b) identifying the residues of a peptide that contribute to fibril formation by mutating any amino acid sequence of the protein and interacting the peptide with the cell to inhibit fibril formation, and (7) the method for minimizing the aggregation tendencies of human kappa-IV immunoglobulin light chain protein in a cell, the method comprising a) expressing any or all protein in a cell, b) identifying the residues of a peptide that contribute to fibril formation by mutating any amino acid sequence of the protein and interacting the peptide with the cell to inhibit fibril formation wherein the peptide contains an amino acid sequence which is also contained in the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only for a method of minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in *vitro* by identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril formation, synthesizing peptides selected from the group consisting of spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, and determining the V_L-derived peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR (SEQ ID NO: 12) and LTLKLSR (SEEQ ID NO: 13) for their ability to inhibit SMA fibril formation *in vitro*. The specification further discloses a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in a cell, the method comprises identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril aggregation, synthesizing peptides spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, expressing SMA or LEN in COS cells, treating said cells with said peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12) and LTLKLSR (SEQ ID NO: 13) and determining the V_L-derived peptides for their ability to inhibit SMA fibril aggregation in said cell by western blotting or immunoflouresence.

The specification does not teach any of the method mentioned above because there is insufficient guidance as to which particular "submotifs" in the primary structures of all amyloid forming proteins such as antibody constant domains, transthyretin, bta-2microglobulin, serine protease inhibitors and crystalline contribute to fibril formation. Further, there is insufficient

guidance as how to make any or all "biological molecule inhibitor" that interacts with the undisclosed critical "submotifs" for the claimed method. The terms "biological molecule inhibitor" (claim 23) and "biological molecules" (claim 30) without the amino acid sequence or chemical structures have no structure, much less function. Further, the term "having" is open-ended. It expands the peptide inhibitor Phe_{71}-Thr_{72}-Leu-$_{73}$-Thr_{74},-Ile_{75}-Ser_{76}-Ser_{77} (SEQ ID NO: 1) to include additional amino acids at either or both ends. There is insufficient guidance as to which undisclosed amino acids to be added and whether the resulting peptide maintains its inhibitory function, in turn, minimizing the aggregation tendencies of *all* amyloid forming protein. Let alone "preventing" fibril assembly of human kappa-IV immunoglobulin. Further, there is insufficient working examples demonstrating any or all undisclosed biological molecule inhibit the aggregation of any or all amyloid forming proteins.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Given the lack of guidance and insufficient working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NO: 1 that after substitution, deletion, insertion and/or modification will retain both structure and have similar function is unpredictable.

Stevens *et al*, of record, teach that amyloid is a generic term for the primarily extra cellular accumulation of fibrillar protein deposits and there are at least 20 unrelated, normally non-fibrillar proteins are known precursors of amyloid and each is associated with a specific disease (See page 443, in particular). Stevens *et al* further teach that in contrast to other proteins typically associated with amyloidosis, not all patients who overproduce light chains during myeloma experience development of clinically significant deposit, and no examples of light chains that differ at only a single amino acid position have been found today. Given the diversity of antibody light chains, a virtually unlimited number of variations, both inherited and acquired through somatic mutation can account fibril formation (See page 445, column 2, last paragraph, page 446, in particular).

For these reasons, it would take an undue amount of experimentation for even one skilled in the art to practice the claimed invention. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 23-30, 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any or all "submotifs" in the claimed method, (2) any or all "biological molecule inhibitor" for the claimed method of minimizing the aggregation tendencies of all (3) amyloid forming protein, (4) any or all peptide inhibitor "having" the amino acid sequence Phe_{71}-Thr_{72}-Leu-$_{73}$-Thr_{74},-Ile_{75}-Ser_{76}-Ser_{77} (SEQ ID NO: 1) in the claimed method, (5) any or all "biological molecules" for a method of "preventing fibril assembly of human kappa-IV immunoglobulin, (6) any or all "protein" expressing in a cell, and mutating the amino acid sequence of any or all protein in the method for minimizing the aggregation tendencies of human kappa-IV immunoglobulin light chain protein.

The specification discloses only for a method of minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in *vitro* by identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril formation, synthesizing peptides selected from the group consisting of spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, and determining the V_L-derived peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR (SEQ ID NO: 12) and LTLKLSR (SEEQ ID NO: 13) for their ability to inhibit SMA fibril formation *in vitro*. The specification further discloses a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in a cell, the method comprises identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each

SMA mutation into LEN to identify the residues of a peptide that contribute to fibril aggregation, synthesizing peptides spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, expressing SMA or LEN in COS cells, treating said cells with said peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12) and LTLKLSR (SEQ ID NO: 13) and determining the V_L-derived peptides for their ability to inhibit SMA fibril aggregation in said cell by western blotting or immunoflouresence.

With the exception of the specific Greek key motif for the specific method, there is inadequate written description about any or all "submotifs" for the claimed method.

Other than the specific peptide inhibitors and the specific human kappa-4 immunoglobulin light chain (LC) to be mutated for a method minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC), there is inadequate written description about the structure associated with function of any other "biological molecule inhibitor" and "biological molecules" without the chemical structure or amino acid sequence.

Regarding to any peptide inhibitor "having" the amino acid sequence Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74},-Ile_{75}-Ser_{76}-Ser_{77} (SEQ ID NO: 1) in the claimed method, the term "having" is open-ended. It expands the peptide inhibitor Phe_{71}-Thr_{72}-Leu_{73}-Thr_{74},-Ile_{75}-Ser_{76}-Ser_{77} (SEQ ID NO: 1) to include additional amino acids at either or both ends to read on the full-length polypeptide. Further, there is insufficient written description about which undisclosed amino acids to be added and whether the resulting peptide maintains its inhibitory function, in turn, minimizing the aggregation tendencies of all amyloid forming protein or "preventing" fibril assembly of human kappa-IV immunoglobulin.

As for any or all "protein" expressing in a cell (claim 32), there is inadequate written description about which protein to be expressed in a cell and interacting with which "peptide" to inhibit fibril formation for the claimed method.

Given the lack of a written description of *any* additional representative species of "biological molecule inhibitor", "biological molecules" and peptide derived from other amyloid forming protein or Greek key fold protein such as transthyretin, beta-2 microglobulins, any serine protease inhibitors and crystalline for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California*

v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. Claims 26-27 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "...60 and 83 of the light chain" in Claim 26 represents a departure from the specification and the claims as originally filed. It would be helpful if applicants would point out where in the specification that term at issue may be found.

The "submotifs in primary structures of the protein" in claim 23 represents a departure from the specification and the claims as originally filed. The specification describes only Greek key motif.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 15-16, 23-24, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "Phe_{71}-Thr_{72}-Leu-$_{73}$-Thr_{74},-Ile_{75}-Ser_{76}-Ser_{77} wherein the subscripts numbers indicate the residue location **on the domain**" in claim 15 is ambiguous and indefinite because the subscript denotes the amino acid residues of the full-length human kappa-IV light chain.

The "Phe_{71}-Thr_{72}-Leu-$_{73}$-Thr_{74},-Ile_{75}-Ser_{76}-Ser_{77} wherein the subscripts denote the positions of the amino acids in the **residue**" in claim 27 is ambiguous and infinite. It is not clear what is meant by in the residue. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "submotifs in primary structures of the protein" in claim 23 is ambiguous and indefinite because there is only one primary structure per protein. Further, it is not which particular "submotifs" that one of ordinary skill must identify in the claimed method.

The "step of identifying submotifs comprises mutating the amino acid sequence of said protein" in claim 24 is ambiguous because it is not clear how mutating the amino acid sequence in the protein relates to the step of identifying submotifs in addition to which amino acid within the protein is to be mutated from which amino acid to which amino acid. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 23-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Boland *et al* (J Biol Chem 271: 18032-18044, 1996; PTO 892).

Boland *et al* teach a method for minimizing the aggregation of an amyloid forming protein such as amyloid-β peptide, the reference method comprises identifying submotifs such as peptapeptide sequence in primary sequence or amino acid sequence such as GSNKGAIIGLM of amyloid-β peptide and serine protease inhibitor such as α1-antitrypsin (See page 18032, col. 2, second paragraph, in particular) and exposing various biological molecule inhibitors such as α1-At chimeric peptide amβ/α1AT (GSNKGAFVFLM) and α1AT/amβ (VKFNKPIIGLM), and peptide 105Y (SIPPEVKFNKPFVFLM) (See page 18037, in particular) to see whether it stabilizes the normal conformation of the protein (see entire document, Fig 4, in particular). Boland *et al* teach identifying motifs by mutating the amino acid sequence of the reference amyloid-β peptide such as swapping domain 2 amino acids, GA from amyloid-β 25-35 for P from α1AT (See page 18039, col. 1, second paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 23, 25, 29-30, 32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boland *et al* (J Biol Chem 271: 18032-18044, 1996; PTO 892) in view of Peterson et al (Proc Natl Acad Sci USA 95: 12956-12960, Oct 1998; PTO 892), Davids *et al* (of record, J Immunology 163: 3842-50, Oct 1999; PTO 892), Gardner *et al* (of record, J Biol Chem 268(34): 25940-47, 1993; PTO 892), Schubert *et al* (of record, European J Neuroscience 9: 770-777, 1997; PTO 892) or Ohashi *et al* (of record, Virchows Arch 428(1): 37-46, 1996; PTO 892).

The teachings of Boland et al have been discussed supra.

The invention in claim 25 differs from the teachings of the reference only in that the method wherein the protein is transthyretin, human kappa-IV light chain variable domain, or beta-2 microglobulin.

The invention in claim 29 differs from the teachings of the reference only in that the method wherein the inhibitor is a serine protease inhibitor.

The invention in claim 30 differs from the teachings of the reference only in that a method of preventing fibril assembly of human kappa-IV immunoglobulin instead of any amyloid forming protein.

The invention in claim 32 differs from the teachings of the reference only in that a method of preventing fibril assembly of human kappa-IV immunoglobulin in a cell instead of any amyloid forming protein comprising expressing the protein in a cell; identifying the residues of a

peptide that contribute to fibril formation by mutating the amino acid sequence of the protein and interacting the peptide with the cell to inhibit fibril formation.

The invention in claim 34 differs from the teachings of the reference only in that a method of preventing fibril assembly of human kappa-IV immunoglobulin in a cell wherein the peptide contains an amino acid sequence which is also contain in the human kappa-IV immunoglobulin.

Peterson *et al* teach a method of screening for inhibitor that inhibits or stabilizes transthyretin conformational change that lead to amyloid fibril formation by using established amyloid firbril assays. Active compounds such as thyroid hormone and derivatives thereofy strongly stabilize the normal native conformation of transthyretin and inhibit wild type, V30M, and L55P mutations associated with amyloid formation under partially denaturing condition such as when the amyloid forming protein is partially unfold (See page 12956, col. 2, 3rd paragraph, in particular). Peterson *et al* small molecule inhibitor that stabilizes the normal conformation of a protein is desirable as a possible approach to treat amyloid diseases (See abstract, in particular).

Davids *et al* teach mutation in the amino acid sequence of the human immunoglobulin kappa IV light chain variable domain such as LEN k chain and SMA and REC kappa chain resulted in amyloidosis (See page 3844, col. 2, last paragraph, in particular).

Gardner *et al* teach a serine protease inhibitor such as 3,4-DCI that protects newly synthesized immunoglobulin light chain from degradation (See page 25944, column 2, k Chain Degradation Is Inhibited by Serine Protease Inhibitors, Fig 8, in particular).

Schubert *et al* teach a serine protease inhibitor such as Serpins that inhibits amyloid peptides aggregation and toxicity (See entire document, page 771, column 2, Serpins inhibits amyloid and amylin toxicity and aggregation, in particular).

Ohashi *et al* teach beta-2-microglobulin amyloidosis associated with long-term heamodialysis which has an increased in matrix metalloproteinases such as MMP-1, while AL amyloidosis is involved in immunoglobulin light chain deposits in the particular tissues (See abstract, page 44, column 2, in particular). Ohashi *et al* teach serine proteinases have been implicated in the degradation of extracellular matrix components and various proteinase inhibitors are useful for inhibiting joint destruction (See page 37, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the amyloid-β forming protein as taught by Boland *et al* for the transthyretin protein as taught by Peterson *et al,* or the human immunoglobulin kappa IV light

chain variable domain as taught by Davids *et al* or the beta-2-microglobulin that have a tendency to aggregate to form amyloid as taught by Ohashi *et al* in the method for minimizing the aggregation tendencies of amyloid forming protein as taught by Boland by testing the biological inhibitor such as serine protease inhibitor as taught Gardner *et al* or Schubert *et al* to the see whether it minimizing the aggregation tendencies of said amyloid forming proteins. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Peterson *et al* small molecule inhibitor that stabilizes the normal conformation of a protein is desirable as a possible approach to treat amyloid diseases (See abstract, in particular). Davids *et al* teach mutation in the amino acid sequence of the human immunoglobulin kappa IV light chain variable domain such as LEN k chain and SMA and REC kappa chain resulted in amyloidosis (See page 3844, col. 2, last paragraph, in particular). Gardner *et al* teach serine protease inhibitor such as 3,4-DCI can protect newly synthesized immunoglobulin light chain from degradation (See page 25944, column 2, k Chain Degradation Is Inhibited by Serine Protease Inhibitors, Fig 8, in particular). Schubert *et al* teach serine protease inhibitor such as Serpins can inhibit amyloid peptides aggregation and toxicity (See entire document, page 771, column 2, Serpins inhibits amyloid and amylin toxicity and aggregation, in particular). Ohashi *et al* teach serine proteinases have been implicated in the degradation of extracellular matrix components and various proteinase inhibitors are useful for inhibiting joint destruction and beta-2-microglobulin amyloidosis associated with long-term heamodialysis that has an increased in matrix metalloproteinases such as MMP-1 (See page 37, column 2, in particular).

17. Claims 1-2, 5, 7 and 10 are allowed.

18. Claims 31 and 33 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The

examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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June 14, 2004

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